REMARKS/ARGUMENTS

Reconsideration and continued examination of the above-identified application are respectfully requested.

No claims have been amended by way of this amendment.

Interview with the Examiner

The applicants appreciate the telephone interview between the applicants' representative and Examiner Goldberg on October 8, 2008. During the interview, the applicants' representative discussed possible claim amendments. The Examiner stated that submitting information which shows a decrease in enzyme activity for the 9 isoforms mentioned in the claim would help to overcome the rejection.

Rejection of claims 1-2, 5-6, 10, 13, and 19-21 under 35 U.S.C. §112 -- first paragraph

At pages 2-3 of the Office Action, the Examiner rejects claims 1-2, 5-6, 10, 13, and 19-21 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. For essentially the same reasons set forth in the previous Office Action, the Examiner states that Kurkela et al. shows that there is no predictability between isoforms and different drugs. The Examiner states that Kurkela et al. compares the 1A9 and 1A6 isoforms and finds differences in the effect of the Y483D mutation between the two isoforms (page 2448, column 2). This rejection is respectfully traversed.

Contrary to the Examiner's suggestion, none of the findings in Kurkela et al. are inconsistent with the scope of the present claims or the teachings of the present application. Kurkela et al. describes the effect of the Y483D mutation between the 1A9 isoforms and 1A6

isoforms of UGT1. Kurkela et al. states that the Tyr to Asp mutation causes different effects on the enzymatic activity in scopoletin glucuronidation between UGT1A9 and UGT1A6. Unlike the present claims, Kurkela et al. does not describe any glucuronidation of 2-amino-5-nitro-4-trifluoromethylphenol. Also, unlike the present claims, Kurkela et al. also does not describe any glucuronidation by UGT1A1. Thus, the findings in Kurkela et al. do not relate in any way to the present claims. As the scope of the present claims and Kurkela et al. are unrelated, the present claims do not contradict any of the findings described in Kurkela et al. Thus, Kurkela et al. cannot properly be relied upon to dispute enablement of the present claims.

It should also be noted that the findings of the present inventors are consistent with what is generally known in the art today. Based on numerous studies on the effect of mutation at different positions in isoforms of UGT1 on enzymatic activity, it has been found that mutation generally decreases the enzymatic activity of UGT1 isoforms, for example, UGT1A4 and UGT1A7. In fact, an increase in enzymatic activity of UGT1 by the mutation rarely occurs. To further illustrate this, the applicants respectfully request the Examiner to consider the findings described in Guillemette et al. ("Structural heterogeneity at the UDP-glucuronosyltransferase 1 locus: functional consequences of three novel missense mutations in the human *UGT1A7* gene," PHARMACOGENETICS, Vol. 10(7), pages 629-644, October 2000), attached herewith. Guillemette et al. states that mutations in the UGT1A7 gene confer slow glucuronidation phenotype (Abstract). Guillemette et al. compares the glucuronidating activities of UGT1A7 wild type and UGT1A7 variants and concludes that the enzymatic activity of the variants is less than the enzymatic activity of the wild type (Table 4). Table 4 from Guillemette et al. is provided below, in order to assist the Examiner.

Table 4. Relative glucuronidating activities of UGT1A7 variants towards B(a)P phenols

Cell population	*UGT activity (pmol/mg/h)*					
	3-OH-B(a)P		*7-OH-B(a)P*		*9-OH-B(a)P*	
	Absolute	*Relative*	*Absolute*	*Relative*	*Absolute*	*Relative*
Untransfected	ND	–	ND	–	ND	–
**1*	50.5 ± 2	315 ± 10[a] (3.4)	263 ± 3	1645 ± 19[a] (3.6)	20 ± 1	125 ± 6[a] (3.7)
**2*	108 ± 2	166 ± 3[b] (1.8)	579 ± 16	890 ± 25[b] (2.0)	41 ± 2	62 ± 4[b] (1.8)
**3*	93 ± 4	93 ± 4 (1.0)	450 ± 21	450 ± 21 (1.0)	34 ± 2	34 ± 2 (1.0)
**4*	59.5 ± 2	123 ± 35 (1.3)	275 ± 10	572 ± 20 (1.3)	20 ± 1	42 ± 2 (1.2)

Glucuronidating activities of UGT1A7 variant-expressing HEK cell membranes were determined towards the indicated B(a)P phenol substrates. The data shown represent the mean ± SD of three determinations. The relative B(a)P phenol UGT activities of the variants were calculated by dividing the absolute activities by the corresponding fractional level of expressed UGT1A7 determined by immunoblot analysis (0.16 for **1*, 0.64 for **2*, 1.0 for **3*, and 0.48 for **4*). Values in parentheses represent the ratio of the mean to that of the **3* cell population. [a]$P \leq 0.01$ *vs.* **2* group. [b]$P \leq 0.02$ *vs.* **3* group. ND, not detected.

In table 4, *1, *2, *3 and *4 indicate wild type, double mutant with N129K and R131K, triple mutant with N129K, R131K and W208R, single mutant with W208R, respectively. 3-OH-B(a)P, 7-OH-B(a)P and 9-OH-B(a)P are the substrates for the enzyme assay. The Relative values are the corrected values obtained by dividing the Absolute value by the amount of corresponding expressed protein. The Relative values are appropriate for describing the enzymatic activity of the protein. As can be seen, enzymatic activity of the variants is less than the enzymatic activity of the wild type. For example, single mutant with W208R (*4) shows decreased enzymatic activity compared with wild type (*1).

This evidence further supports the applicants' position in this matter and, further, is more on point to the subject matter of the claimed invention than the Examiner's relied upon article of Kurkela et al. The applicants' evidence/article would therefore be more controlling on this §112 issue.

Accordingly, the rejection should be withdrawn.

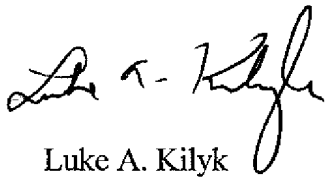
CONCLUSION

In view of the foregoing remarks, the applicant respectfully requests the reconsideration of

this application and the timely allowance of the pending claims.

If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0925. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such extension is requested and should also be charged to said Deposit Account.

Respectfully submitted,



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Attachment: Guillemette et al., "Structural heterogeneity at the UDP-glucuronosyltransferase 1 locus: functional consequences of three novel missense mutations in the human *UGT1A7* gene," PHARMACOGENETICS, Vol. 10(7), pages 629-644, October 2000 (16 pages)